AM-100802

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No: 10/626,943 Confirmation No.: 3231

Applicant: Rubino et al

Filed: July 25, 2003

Art Unit: 1609

Examiner: Polansky, Gregg

Customer No. : 38199

Title: PARENTERAL CCI-779 FORMULATIONS CONTAINING COSOLVENTS, AN ANTIOXIDANT, AND A SURFACTANT (As Amended)

Mail Stop Amendment
Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 CFR 1.131

Sir:

1. I am a co-inventor of the subject matter claimed in the above-identified application.

2. The present application has an effective filing date and thus, at least a constructive reduction to practice, of July 30, 2002.

3. The subject matter of certain claims in the present application have been rejected, in an Office Action dated March 17, 2008, under 35 USC 103(a) on the basis of US Published Patent Application No. 2002/0013335A1, which published January 31, 2002. The publication date of the PCT counterpart of the Azrolan application [WO01/97809] was December 27, 2001. These publications were less than one year before the effective priority date of this application.

4. This Declaration is being submitted to establish that the invention was made earlier than December 27, 2001.

5. Applicants conceived the present invention prior to December 27, 2001 in the United States. Copies of relevant portions of a Record of Invention for this invention are provided to supply evidence of the conception of the present invention. The Record of Invention has been redacted to remove the date of submission to the Patent Law Department of assignee. The date of submission of the Record of Invention was prior to December 27, 2001.

6. Work on the present invention continued in the United States with diligence from the date of conception of the invention, which occurred prior to the publication of the cited document, to reduction to practice of the invention.

7. This Declaration is submitted prior to final rejection.

8. As a person signing below, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issues thereon.

Joseph T. Rubino — Date: 04-JUN-2008

Victoria Siskavich — Date: 29 MAY 08

Maureen M. Harrison — Date: 06-JUN-2008

Pooja Gandhi — Date: 29-MAY-2008

AM100802

**** CONFIDENTIAL AND PRIVILEGED ****

AMERICAN HOME PRODUCTS CORPORATION
RECORD OF INVENTION
SMALL MOLECULE INVENTIONS

TO: Patent Law Department
Small Molecule Section
St. Davids, PA 170-3

Submitted by: Joseph T. Rubino
Location: [redacted]
Phone No.:

DATE: [redacted]

1. TITLE OF INVENTION: (Brief, but comprehensive, technically accurate, and descriptive).

Parenteral Dosage Forms of CCI-779

2. DETAILED DESCRIPTION OF THE INVENTION:
Provide a detailed description of the invention on attached sheets, including, as applicable, chemical synthesis, pharmacological testing, and actual example(s) of the invention, and WAY numbers for the compounds covered by this invention record.

See Attached

3. USES / USEFULNESS / ADVANTAGES OF THE INVENTION OVER CURRENTLY AVAILABLE TECHNOLOGY, AND COMMERCIAL APPLICABILITY: Describe the specific use of your invention and how it differs from what is presently available in the field. Identify the advantages and benefits of the invention over the current technology, such as increased efficiency or overcoming a defect. Identify possible new uses of the invention, and its commercial applicability. This may be included as part of the description of the invention. Attach additional sheets if necessary.

See Background and Description

4. PRIOR ART:
On a separate page list all patents, publications, technologies or prior use(s), collectively referred to as "Prior Art", and point out how the invention differs. Copies of all Prior Art must be submitted with the Record of Invention.

See Attached

5. PUBLIC DISCLOSURE / PUBLICATION PLANS: Public disclosure includes abstracts and presentation at scientific meetings, including poster sessions, publications, disclosure to others outside of the Corporation who have not signed a confidentiality agreement, and use, sale, or offer for sale of the invention. Also indicate any future disclosure or publication plans. Attach additional sheets if necessary.

No disclosure has occurred. Plans for future disclosure have not been made.

[redacted]

The concept of the cosolvent concentrate containing CCI-779 combined with a diluent that contains an acceptable surfactant can be used to produce a dosage form that is suitable for administration by either direct injection or by addition to sterile infusion fluids for intravenous infusion. When the drug is given by direct injection, a diluent formulation that is primarily aqueous, as represented by Example 3, would be most suitable. When the drug is administered by addition to sterile infusion solutions, the diluent formulation can be either primarily aqueous or nonaqueous. In the latter case a water miscible cosolvent replaces water in the diluent. Example 4 is a formulation that is nonaqueous and is intended to be added to sterile infusion solutions, such as 0.9% Sodium Chloride Injection, 5% Dextrose Injection, Lactated Ringers Injection, and other commonly used intravenous infusion solutions prior to administration via intravenous infusion.

The cosolvent concentrate containing CCI-779 and the diluent are maintained in separate containers in order to preserve the chemical integrity of CCI-779. Surface active agents, such as polysorbate 80, have been found to accelerate the degradation of CCI-779 over time. However, when the drug and surfactant solution are combined just prior to administration, chemical and physical stability are sufficiently good to permit a useful period of time (i.e. several hours to a day) for administration of the drug.

Examples of formulations of CCI-779 for intravenous administration are given below:

Example 1:

CCI-779 25 mg
Citric acid, anhydrous 0.005%
Dehydrated alcohol, USP q.s. 1.0 ml

The above formula is packaged in a glass ampule with a nitrogen/air headspace and has a shelf-life of 18 months to 2 years when stored at 2-8 °C

Example 2: ✓

CCI-779	25 mg
dehydrated alcohol, USP	0.395 g.
d,l-α-tocopherol, USP	0.75 mg
propylene glycol, USP, q.s.	1.0 mL

The above formula was packaged in a vial with a nitrogen/air headspace. It has demonstrated good stability after 9 months storage at 2-8 °C and room temperature. No significant degradation has been observed after 9 months at 5 °C. The stability continues to be monitored.

Both formulae presented in Examples 1 and 2 can be sterilized by aseptic filtration.

The following are examples of diluent formulae:

Example 3:

Polysorbate 80, NF 5% w/v
Polyethylene glycol 400 NF 5%w/v
Water for Injection, USP q.s. 100%

This formula can be packaged in vials, sealed and sterilized by autoclaving.

The above formula is combined in a ratio of 9:1 with example 1 or 2 to produce a solution of CCI-779 at a concentration of 2.5 mg/ml. The resulting mixture can be injected directly or further diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to provide a solution for intravenous infusion. Such mixtures are physically and chemically stable for several hours at room temperature. The above diluent, when combined with the CCI-779 formulations in Examples 1 and 2, have been used to deliver doses of 0.5 to 500 mg CCI-779 via direct intravenous injection or intravenous infusion.

Example 4: ✓

Polysorbate 80, NF 33.3%w/v
Dehydrated alcohol, USP 19.9%w/v
Polyethylene glycol 400, NF q.s. 100%

This formula is sterilized by aseptic filtration.

The above formula can be combined with Example 1 or 2 in a ratio of 1.5:1 to produce a solution containing 10 mg/ml CCI-779. This can be further diluted with 0.9% Sodium Chloride injection or 5% Dextrose Injection to provide a solution for intravenous infusion. These mixtures are physically and chemically stable for several hours at room temperature. The above diluent, when combined with the CCI-779 formulations in Examples 1 and 2, are useful for delivering doses of 2 to 500 mg via intravenous infusion.

In summary, dosage forms of CCI-779 have been described that are suitable for intravenous administration. The physical and chemical integrity of the drug are preserved by a combination of parenterally acceptable cosolvents, antioxidants and surfactants, the latter being combined with the drug solution just prior to administration. These dosage forms are easy to produce and only require standard equipment commonly used in all parenteral production facilities. When added to intravenous infusion fluids, a clear solution is formed that permits easy inspection of the contents prior to administration and has sufficient physical and chemical stability to permit convenient administration.